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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/284,009	04/05/1999	CLAIRE F. LEWIS	550-128	1771

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	16

DATE MAILED: 08/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/284,009	LEWIS ET AL.	
	Examiner	Art Unit	
	Celine qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2002*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *87-126* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *87-126* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

1. ☒ Notice of References Cited, PTO-892.
2. ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948.
4. ☐ Interview Summary, PTO-413, Paper No(s). _____
5. ☐ Notice of Informal Patent Application, PTO-152.

DETAILED ACTION

Claims 87-126 are pending in the application.

This Office Action is in response to the Amendment filed on 4/29/02.

Response to Amendment

The rejection of claims 69-73, 81 and 82 under 35 U.S.C. 112, first paragraph has been withdrawn in light of Applicants cancellation of the claims.

The rejection of claims 51-85 under 35 U.S.C. 112, second paragraph has been withdrawn in light of Applicants cancellation of the claims.

The rejection of claims 51-53, 56, 60-65, 68 and 70 under 35 U.S.C. 101 has been withdrawn in light of Applicants cancellation of the claims.

The rejection of claims 51-54 and 68 under 35 U.S.C. 102 (b) has been withdrawn in light of Applicants cancellation of the claims.

The rejection of claims 51-68, 74-80 and 83-86 under 35 U.S.C. 103 (a) has been withdrawn in light of Applicants cancellation of the claims.

The objection of claims has been withdrawn in light of Applicants cancellation of the claims.

Claims 87-126 are rejected under 35 U.S.C. 112, first paragraph for reasons set forth below.

Claims 90, 94 and 101-103 are rejected under 35 U.S.C.112, second paragraph for reasons set forth below.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

Claims 87-126 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

The nature of the invention is a construct comprising one or more hypoxia or ischemic or stress regulatable element operably linked to one or more nucleotide sequence of interest, wherein the construct is coupled to a binding agent that is capable of binding to cell surface element of a mononuclear phagocyte (111-115, 125). The claims are further drawn to a mononuclear phagocyte modified to comprise said construct and a pharmaceutical composition comprising said mononuclear phagocyte (87-104, 110, 120-124). The claims are further directed

mononuclear phagocytes in vitro or in vivo (106); (iv) a delivery system for targeting a mononuclear phagocyte to a target hypoxic, ischemic or stress site, or any combination of hypoxia, ischemia and stress sites (109); and (v) internalizing a regulatable agent into a phagocyte (116).

The claims are considered not enabled for the same reasons set forth in the prior office action mailed on 11/28/01 (see pages 3-9). In response to Applicants' argument that the specification provides extensive guidance on the preparation of the mononuclear phagocytes and the methods of gene transfer is well known in the art, the Examiner agrees that such mononuclear phagocytes comprising exogenous construct can be prepared ex vivo, however, the enablement rejection is based on how to use said phagocytes and constructs based on the disclosure of the specification. The specification prophetically states that the constructs and phagocytes can be used in control of vascularization of developing tissues so as to promote vascularization, or directed to damaged to the vascular system via an amputation, stroke, cardiac arrest, extreme hypertension, ischemia and burns. The specification further states that the expression of said construct in phagocytes in tumor hypoxic condition can be used to deliver prodrug or agents having cytotoxic effect to tumor cells in vivo. For such disclosed uses, the claimed invention is not enabled because the specification fails to teach a method of in vivo gene therapy that would overcome the technical difficulties discussed in the prior office action (see page 6, 2nd and 3rd paragraph)

Applicants further argue that the "sustained expression" of the gene of interest can be

the exogenous introduced monocytes/macrophages would be able to compete with the endogenous monocytes/macrophages and infiltrate to the hypoxic sites and reach therapeutic effective amount of "sustained expression" is unpredictable. Especially when take in to account factors such as host immune response to viral vectors (see Verma, page 241, 1st col., 4th paragraph) and host immune response to monocytes from different species (see page 6, 1st paragraph).

Applicants further argue that nude mice is a relevant model for studying human tumor because first, a scaleable process needs to be established that can be translated to human application; second, gene therapy techniques may be performed in conjunction with at least some degree of immunosuppressive treatment to maximize the success of the therapy; third, "bubble boy" story, a single success in treating SCID by transplanting bone marrow comprising a corrected gene.

In response to the above arguments, the Examiner agrees that nude mouse is a valid experimental model, however, considering the claims encompass methods for in vivo gene therapy in all kinds of animals having wide range of host immune system, including fully immune functional human, the success in an immuno-deficient mouse model cannot predict the success in other animals which possesses such complex immune defense system. Although gene therapy may be performed with some degree of immunosuppressive treatment, such treatment does not totally comprise the host immune system as those in nude mice. Moreover, the goal of gene therapy is to achieve high expression through manipulation of the vector but not the patient

immuno-deficient. In addition, there is the issue of safety and efficacy of the therapeutic effect of the gene. As Crystal points out that humans are not simply large mice (see page 409, 1st and 2nd col), the author specifically discusses an ex vivo-in vivo strategy to treat glioblastoma, transfer of xenogenic retrovirus-producing cells to the tumor was accomplished without significant adverse effects in animals, but the human studies have been associated with nervous system toxicity related to transfer of the cell line to the tumor.

The supplemental data provided in the Declaration of Stuart Naylor has been fully considered. However, these experiments are all performed in nude mouse model. For reasons discussed above, it cannot predict the success in human trial. Therefore, it is not sufficient to overcome the enablement rejection.

Therefore, in view of the technical difficulties in gene therapy as discussed above and in the prior office action, one skilled in the art has to turn to the specification for guidance to practice the invention. However, the specification does not provide teachings and working examples on how to overcome these technical difficulties. As such, one skilled in the art would have to engage in undue amount of experimentation to practice the invention as claimed.

Claims 90, 94, 101-103 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 90, the phrase "preferably" renders the claim indefinite because it is

Claim 94 recites the limitation "lentiviral vector" in 2. There is insufficient antecedent basis for this limitation in the claim. The parent claim 92 does not recite such limitation.

Regarding claims 101-103, the term "activating or control product" renders the claims indefinite because it is unclear what this product activates or controls. As such, the metes and bounds of the claims cannot be established.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D
August 26, 2002

SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600